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ning of each regular issue of the PCT Gazette.



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(54) Title: METHODS AND COMPOUNDS FOR INHIBITING AMYLOID DEPOSITS

(57) Abstract: Methods and compositions which are useful in the treatment of amyloidosis. In particular, methods and compositions are provided for inhibiting, preventing and treating amyloid deposition, e.g., in pancreatic islets, wherein the amyloidotic deposits are islet amyloid polypeptide (IAPP)-associated amyloid deposition or deposits. The methods of the invention involve administering to a subject a therapeutic compound which inhibits IAPP-associated amyloid deposits. Accordingly, the compositions and methods of the invention are useful for inhibiting IAPP-associated amyloidosis in disorders in which such amyloid deposition occurs, such as diabetes.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/472 A61K31/675 A61K31/4725 A61K31/706
A61K31/4741 A61K31/473 A61K31/47 A61K31/4709 A61K31/185
A61K31/194 A61K31/192 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 03680 A (FRASER PAUL ;NEUROCHEM INC (CA); SZAREK WALTER (CA); WEAVER DONALD) 18 January 2001 (2001-01-18) abstract; claims; examples ---	1-31
E	WO 00 64420 A (KONG XIANQI ;NEUROCHEM INC (CA); SZAREK WALTER (CA); UNIV KINGSTON) 2 November 2000 (2000-11-02) abstract page 2, line 15 -page 4, line 25 page 12, line 17 -page 16, line 13 page 22, line 21 -page 23, line 5; claims 1-11,37-53; figures; examples 6,7,9 --- -/--	1-31

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 00 57707 A (PROTEOTECH INC) 5 October 2000 (2000-10-05)</p> <p>abstract page 1, line 1 -page 2, line 9 page 3, line 4 -page 4, line 3 page 5, line 19 - line 24; claims 1,11,12,14; example 6 ---</p>	1,6,7, 12,17, 22,31
P,X	<p>WO 00 06133 A (NEUROCHEM INC ;UNIV KINGSTON (CA)) 10 February 2000 (2000-02-10) abstract page 2, line 8 -page 4, line 30 page 42 page 48 -page 49; claims; figures 1-4,10 ---</p>	8-11, 27-30
X	<p>WO 96 28187 A (KISILEVSKY ROBERT ;SZAREK WALTER (CA); UNIV KINGSTON (CA); WEAVER) 19 September 1996 (1996-09-19)</p> <p>the whole document, in particular page 20, lines 15-27; figure 10, compounds XXVII,XXX,XXXII ---</p>	1-3,6-9, 12-14, 17-19, 22-24, 27,28,31
X	<p>POWELL D S (REPRINT) ET AL: "Insulin and polyionic sulphonates modify human islet amyloid polypeptide fibril aggregation in vitro" DIABETOLOGIA, (AUG 1998) VOL. 41, SUPP. [1], PP. 656-656. PUBLISHER: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0012-186X., XP000978398 RADCLIFFE INFIRM, DIABET RES LABS, OXFORD OX2 6HE, ENGLAND;UNIV OXFORD, DEPT HUMAN ANAT, OXFORD OX1 3QX, ENGLAND; UNIV TORONTO, CNDR, TORONTO, ON, CANADA; QUEENS UNIV, DEPT CHEM, KINGSTON, ON K7L 3N6, CANADA the whole document ---</p>	1,6,7, 12,17, 22,31
X	<p>WO 94 22437 A (UNIV KINGSTON) 13 October 1994 (1994-10-13)</p> <p>the whole document, in particular page 15, lines 21-33 --- -/--</p>	1,6,7, 12,17, 22,31

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International Application No

PCT/CA 00/00607

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 164 295 A (KISILEVSKY ROBERT ET AL) 17 November 1992 (1992-11-17) abstract column 1, line 1 - line 53 column 2, line 10 - line 44 column 7, line 25 - line 41; claim 1 ---	1,6,7, 12,17, 22,31
X	WO 97 09976 A (UNIV WASHINGTON) 20 March 1997 (1997-03-20) abstract page 2, line 27 - line 34; claims 1-4 ---	8,9,27, 28
A	WO 96 37612 A (PFIZER ;CARTY MAYNARD D (US); KREUTTER DAVID K (US); SOELLER WALTE) 28 November 1996 (1996-11-28) page 1, line 1 - line 22 page 3, line 18 - line 26; claims 25-31; figures 6,7 ---	1-3,6-9, 12-14, 17-19, 22-24, 27,28,31
A	O'BRIEN T D ET AL: "HUMAN ISLET AMYLOID POLYPEPTIDE EXPRESSION IN COS-1 CELLS A MODEL OF INTRACELLULAR AMYLOIDOGENESIS" AMERICAN JOURNAL OF PATHOLOGY,US,PHILADELPHIA, PA, vol. 147, no. 3, 1 September 1995 (1995-09-01), pages 609-616, XP000590832 ISSN: 0002-9440 the whole document ---	1-3,6-9, 12-14, 17-19, 22-24, 27,28,31
X	DE 43 13 118 A (HOECHST AG) 27 October 1994 (1994-10-27) the whole document ---	10,11,29
X	GEORGIEV, V. S. ET AL: "Drug-induced modifications of the immune response. 1. Substituted 1-phenylisoquinolines" J. MED. CHEM. (1979), 22(4), 348-52 , XP000992891 the whole document, in particular compound 25 ---	10,11, 29,30
X	US 3 872 125 A (HOULIHAN WILLIAM J ET AL) 18 March 1975 (1975-03-18) the whole document ---	10,29
A		4,5,15, 16,20, 21,25,26

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 236 251 A (UNIV PASTEUR) 9 September 1987 (1987-09-09) abstract; claims 1,10,17; examples	10,29
A	---	4,5,15, 16,20, 21,25,26
A	BAURES, PAUL W. ET AL: "Discovering transthyretin amyloid fibril inhibitors by limited screening" BIOORG. MED. CHEM. (1998), 6(8), 1389-1401 XP002129747 abstract; figure 1 ---	4,5,15, 16,20, 21,25,26
A	MALMUSI L ET AL: "1,2,3,4-TETRAHYDROISOQUINOLINE AND RELATED ANALOGS OF THE PHENYLALKYLAMINE DESIGNER DRUG MDMA" MEDICINAL CHEMISTRY RESEARCH, BIRKHAUSER, BOSTON, US, vol. 6, no. 6, 1996, pages 412-426, XP000978322 ISSN: 1054-2523 abstract; table 2 -----	10,11, 29,30

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-7,12-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1(partially),2,3,6(partially),7(partially),8,9,12(partially),
13,14,17(partially),18,19,22(partially),23,24,27,28,31(partially)

Method for inhibiting IAPP-associated amyloid deposits with an
IAPP-inhibiting compound such as defined in claims 2-3 and composition
thereof.

2. Claims: 1(partially),4,5,6(partially),7(partially),10,11,12(partially),
15,16,17(partially),20,21,22(partially),25,26,29,30,31(partially)

Method for inhibiting IAPP-associated amyloid deposits with an
an IAPP-inhibiting compound such as defined in claims 4-5 and composition
thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,6,7,12,17,22,31 relate to a compound defined by reference to a desirable characteristic or property, namely "IAPP-inhibiting compound".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claims 2,4,8,10,13,15,18,20,23,25,27,29 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in FIGs 1-14, and to 1,2,3,4-tetrahydroisoquinoline derivatives, with due regard to the general idea underlying the present invention.

Claims searched completely: 3,5,9,11,14,16,19,21,24,26,28,30

Claims searched incompletely:

1-2,4,6-8,10,12,13,15,17,18,20,22,23,25,27,29,31

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/00607

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0103680	A	18-01-2001	NONE
WO 0064420	A	02-11-2000	AU 4282400 A 10-11-2000 AU 4905000 A 12-12-2000 WO 0071101 A 30-11-2000
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